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Decompensated hypothyroidism: A review for the emergency clinician

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ABSTRACT

Background: Decompensated hypothyroidism, formerly known as myxedema coma, is an endocrine emergency that commonly presents with altered mental status, as well as hypothermia and depressed vital signs. The condition is often caused by an inciting event, which may lead to significant delays in the diagnosis and management of this disease. Although the incidence is low, this disease is associated with significant morbidity and mortality. Therefore, it is important for emergency clinicians to be aware of this condition.
Objective: This narrative review evaluates the emergency medicine diagnosis and management of adult patients with decompensated hypothyroidism.
Discussion: Decompensated hypothyroidism is a severe hypothyroid state associated with multiple organ failure. The diagnosis can be challenging due to similarities with more common diseases and lack of consideration of the diagnosis. Many patients may present with altered sensorium or depressed vital signs. Clinicians should obtain a thyroid stimulating hormone and free thyroxine level when considering the diagnosis. Management involves resuscitation, early steroid supplementation, thyroid hormone replacement, and treatment of the inciting event.
Conclusions: Decompensated hypothyroidism should be considered in the evaluation of patients with altered sensorium and depressed vital signs so as to not miss this critical diagnosis.

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1. Introduction

1.1. Epidemiology

Decompensated hypothyroidism, formerly known as myxedema coma, is a dangerous condition associated with profound thyroid dysfunction. It is a rare condition, with an incidence of 0.22–1.08 cases per million patients per year [1,2]. The most common population affected is women over 60 years of age, especially in those with a previous history of hypothyroidism [1,2]. Worldwide, hypothyroidism is most commonly a result of insufficient iodine intake [3]. However, in areas with sufficient iodine intake, hypothyroidism is most commonly a result of autoimmune thyroiditis, commonly Hashimoto's thyroiditis [3]. Severe hypothyroidism can be difficult to detect due to its similarities with other more common conditions as well as its subtle clinical manifestations. It can occur in concert with or as a result of a number of comorbidities and concomitant infections. Adding to the difficulty of identifying the subtle manifestations, one study found that the majority of cases of decompensated hypothyroidism presented in the winter creating challenges with differentiating patients with decompensated hypothyroidism from those with hypothermia due to an environmental etiology [4]. Due to delays in the diagnosis and management, mortality ranges between 30 and 60% [1,5]. Factors associated with increased mortality include older age (> 65 years), coma, cardiac complications, sepsis, hemodynamic instability, need for doses of liothyronine over 75 micrograms per day, and requirement for mechanical ventilation [1,6,7]. Because the clinical presentation can be challenging and the disease has a high mortality rate, it is essential for emergency medicine (EM) clinicians to be aware of the evaluation and management of this condition.

2. Methods

This narrative review provides a focused overview of decompensated hypothyroidism for emergency clinicians. The authors searched PubMed and Google Scholar for articles using the keywords “myxedema coma” or “decompensated hypothyroidism”. The search was conducted from database inception to April 1, 2020. PubMed yielded 497 articles and Google Scholar yielded 3764 articles. Authors evaluated case reports and series, retrospective and prospective studies, systematic reviews and meta-analyses, and other narrative reviews. Authors also

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reviewed guidelines and supporting citations of included articles. The literature search was restricted to studies published in English, with focus on the EM and critical care literature. Authors decided which studies to include for the review by consensus. When available, systematic reviews and meta-analyses were preferentially selected. These were followed sequentially by randomized controlled trials, prospective studies, retrospective studies, case reports, and other narrative reviews when alternate data were not available. A total of 71 resources were selected for inclusion in this narrative review.

3. Discussion

3.1. Pathophysiology

The thyroid gland is responsible for the secretion of thyroid hormone. Thyroid gland function is primarily regulated by the hypothalamic-pituitary-thyroid (HPT) axis (Fig. 1). The HPT axis has several feedback mechanisms in place that regulate the secretion of thyroid hormone (Fig. 1). The hypothalamus releases thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to secrete thyroid-stimulating hormone (TSH) [8]. Thyroid-stimulating hormone then triggers the thyroid gland to secrete thyroid hormones [8]. The two thyroid hormones released, T3 and T4, are responsible for a number of physiologic responses centered around metabolism and affect nearly every organ system [8]. The ratio of production of total T4 to T3 by the thyroid gland ranges from 13:1 to 16:1 [9-11]. T3 and T4 are generally attached to thyroglobulin, a binding protein, in the serum [12]. T4 is an inactive form that is acted upon by a deiodinase enzyme to form the more active T3 [8]. More than 80% of circulating T3 is formed from the deiodination of T4 by the target tissue [13]. The thyroid hormones then provide feedback to the HPT axis, inhibiting the release of TRH and TSH when sufficient thyroid hormone is present in the circulation [14].

Any insult to an organ involved in the HPT axis can lead to the development of hypothyroidism, such as non-compliance with thyroid replacement therapy in patients with hypothyroidism or Sheehan's syndrome affecting pituitary function [15-17]. There are two forms of hypothyroidism: primary and secondary. Primary hypothyroidism occurs due to an inherent thyroid problem resulting in decreased or absent thyroid hormone production. This decrease in circulating thyroid hormone causes the hypothalamus and pituitary to secrete more TRH and TSH. This is the most common form of hypothyroidism, accounting for approximately 82%–95% of cases [7,14,18]. Secondary (also known as central) hypothyroidism occurs with failure of the hypothalamus to release TRH or failure of the pituitary gland to release TSH, thereby decreasing the production of thyroid hormone.

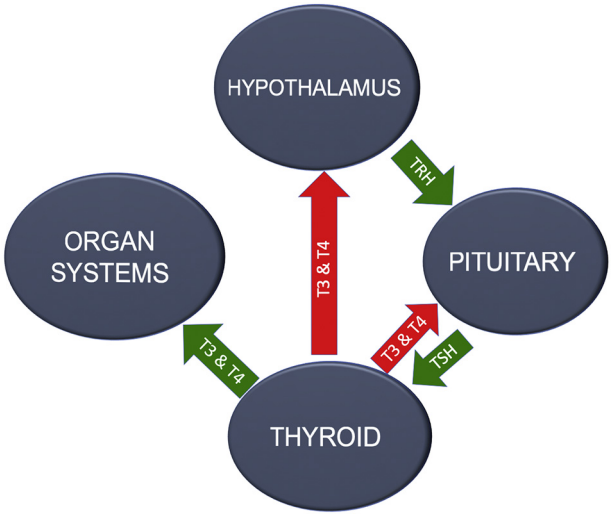

Fig. 1. Hypothalamic-pituitary-thyroid (HPT) axis.

Although decompensated hypothyroidism can occur spontaneously, it is often precipitated by a trigger that overwhelms the HPT axis and leads to profound thyroid dysregulation. Infection is the most common precipitating factor, with the most frequent causes being pneumonia, urinary tract infections, and septicemia [1,6]. In addition to infections, any major stressor on the body can precipitate decompensated hypothyroidism including cerebrovascular accident, gastrointestinal bleed, myocardial infarction, pulmonary embolism, surgery, and trauma [1,19-21]. Medications, such as amiodarone, lithium, and iodinated contrast, can also affect the thyroid gland and its function triggering decompensated hypothyroidism [22-24]. Other medications can induce a profound hypothyroid state in patients already suffering from hypothyroidism leading to decompensated hypothyroidism such as sedatives, opioids, antipsychotics, selective serotonin reuptake inhibitors, phenytoin, beta blockers, diuretics, and chemotherapeutic agents [25-29]. Hypothermia can also cause this, accounting for the increased incidence during the winter months and paucity of cases in tropical locations [30]. Interestingly, ingestion of raw bok choy has also been described. Bok choy contains glucsoinolates which can inhibit thyroid function [31]. Glucosinolates are inactivated by heat; therefore, cooking bok choy prevents this. It is incumbent upon the emergency physician to consider the diagnosis and search for the trigger in patients with decompensated hypothyroidism. However, a case series and reviews have suggested that the precipitating etiology is not identified in 50% of cases [32,33]. Because most of the literature on specific etiologies is limited to case reports and small case series, the true incidence of each cause remains unknown.

3.2. Clinical presentation

Decompensated hypothyroidism often presents nonspecifically and requires a high degree of clinical suspicion. Patients may present with a variety of clinical features, and the term “myxedema coma” may mislead clinicians into believing that they must either have edema or appear comatose in order to have this condition [15]. A better term is decompensated hypothyroidism, which is hypothyroidism that results in organ failure [34]. Decompensated hypothyroidism should be considered in patients who have altered mental status in conjunction with bradycardia, hypotension, and/or hypothermia. Myxedema, or nonpitting edema of the extremities and/or face, may also be present and is caused by lipopolysaccharide deposition; however, this does not occur in all patients [35]. Mental status changes may include confusion, lethargy, stupor, or coma, and may progress over weeks to months [5].

Table 1 provides features of decompensated hypothyroidism separated by organ system. Fig. 2 includes some key features that should raise one's suspicion for decompensated hypothyroidism as well as management priorities. Hypothermia is a common feature, present in approximately 40%–100% of patients based on available literature [1,6,7,32,36]. Bradypnea and hypoventilation can occur due to mental status changes, as well as associated pleural effusions or central hypoventilation [37]. The resultant hypercapnia, which is present in 54% of cases, can further contribute to mental status changes [38,39]. Hypotension and/or bradycardia is also commonly seen in these patients [40,41]. Bradycardia is not universally present, with literature suggesting 54%–88% of patients demonstrate bradycardia on electrocardiogram (ECG) [1,42]. In addition to bradycardia, these patients may experience low output heart failure, which can act in combination with altered vascular permeability to compound cardiovascular decompensation [43]. Patients with very high TSH levels or untreated hypothyroidism are also at increased risk for heart failure [44]. Respiratory failure may result from decreased sensitivity to hypoxia, which is present in 80% of patients, as well as hypercapnia [39]. Pleural effusions and anasarca can occur due to decreased glomerular filtration rate,

Table 1
Organ features of decompensated hypothyroidism [36,37,40,41,43-47]

Cardiovascular	- Bradycardia
	- Pericardial effusion
	- QT prolongation and Torsades de Pointes
	- Diastolic hypertension
	- Heart failure with reduced or preserved ejection fraction
	- Cardiogenic shock
Neurologic	- Confusion, lethargy, stupor, coma
	- Hypoactive delirium, psychosis
	- Delayed relaxation phase of reflexes
	- Seizures
Pulmonary	- Hypoventilation
	- Hypoxia
	- Pleural effusions
Musculoskeletal	- Generalized muscle weakness
	- Rhabdomyolysis
Renal	- Excess ADH secretion
	- Acute kidney injury
	- - Urinary retention
Gastrointestinal	- Nausea and vomiting
	- Constipation
	- Ileus
	- Toxic megacolon
	- Ascites
Hematologic	- Acquired von Willebrand syndrome
	- Coagulopathy from reduction in factors V, VII, VIII, IX, X
	- Anemia
Metabolic	- Hyponatremia
	- Hypothermia
	- Hyperkalemia
	- Refractory hypoglycemia
Dermatologic	- Skin thickening
	- Pretibial myxedema
	- Loss of lateral third of eyebrow
	- Tongue edema

ADH, antidiuretic hormone.

increased capillary permeability, and excess antidiuretic hormone, which will worsen the patient's hemodynamic status [43].

Reflexes in these patients often demonstrate a delayed relaxation phase, which is sometimes referred to as “hung up reflexes” [45]. Patients may develop hypoactive delirium, psychosis, or psychomotor retardation, which has been referred to as “myxedema madness” [46]. Altered mental status is common and found in nearly 100% of patients [1,6,7,32]. As decompensated hypothyroidism more commonly affects the elderly, hypoactive delirium may be a presenting symptom, marked by a change in consciousness and attention with drowsiness and inactivity, often conflated with depression or dementia in this population [47]. Additionally, up to 25% of patients will experience seizures which may progress to status epilepticus, secondary to hypoxia, hypoglycemia, or hyponatremia [48]. Other clinical findings can include constipation, fatigue, skin and hair changes, and loss of the lateral third of the eyebrow [2,49]. A thorough physical examination should include inspection for goiter or surgical scar over the thyroid, as well as assessment for any precipitating event.

3.3. Laboratory testing and imaging

Diagnostic evaluation for decompensated hypothyroidism includes a complete blood count (CBC), electrolytes, liver and renal function, urinalysis, ECG, creatine kinase, venous blood gas, and blood cultures to evaluate for end organ injury and the primary precipitating event [50]. Thyroid function testing, including TSH and free T4, is the mainstay in confirming the diagnosis. An elevated TSH level is an appropriate screening laboratory assay for primary hypothyroidism but can also be low in cases of secondary hypothyroidism. Elevated TSH is present in 81%–100% of patients, and thus normal levels cannot exclude the disease [1,6,7,32]. Of note, severe illness, steroids, and inotropes can also decrease TSH [36]. Therefore, a free T4 level should be ordered with the TSH level, rather than waiting for the TSH results. A low free T4 level is confirmatory for hypothyroidism; T3 may be low but is a late finding and is often of limited additional utility in these patients [51]. Importantly, these laboratory abnormalities should not be used to differentiate decompensated and compensated hypothyroidism, as it is also important to consider the clinical picture. The ECG can demonstrate bradycardia, atrioventricular blocks, low voltage, or a prolonged QT interval [52]. However, data describing frequencies of these findings are limited to case reports and small case series. Thyroid hormone levels may correlate with ECG findings, but literature evaluating this correlation is limited to patients in compensated states [42,52,53]. The CBC may demonstrate leukopenia or a normocytic, normochromic anemia [43]. Creatine kinase can be elevated due to myopathy or rhabdomyolysis [26]. Other common laboratory abnormalities include hyponatremia, hyperkalemia, hypoglycemia, elevated creatinine, and elevated liver transaminases [54].

Imaging should target identifying the precipitating etiology based on history and examination. Patients should receive a chest x-ray to evaluate for suspected pulmonary etiologies and to assess for pleural effusions [37]. Additionally, clinicians should consider a computed tomography of the brain for patients with altered mental status, particularly given the potential for coagulopathy. A point-of-care ultrasound examination can be performed to evaluate for pericardial effusion and pleural effusions. Additional imaging and laboratory investigation should be pursued based on the underlying pathophysiology of potential infection, infarction, or bleeding that caused the decompensation.

3.4. Treatment strategies

Treatment priorities in decompensated hypothyroidism include airway, hemodynamics, managing the underlying etiology, corticosteroid and thyroid hormone administration, and supportive care (Fig. 2). Patients may and often do require mechanical ventilation due to bradypnea and hypopnea, reducing their functional residual capacity [37-39]. These pulmonary derangements generate a hypercapnic and hypoxic state, contributing to the altered mental status as well as creating physiologically-challenging intubations. Because these patients are already hypoxic coupled with decreased functional residual capacity, these patients often have limited oxygen reserve leaving very little apnea time before they become hypoxic. Additionally, patients may also present with anatomical challenges, such as lingual edema, laryngeal edema, or angioedema [55,56]. Pericardial effusions with tamponade physiology may also be present in decompensated hypothyroidism, further complicating the intubation [30,40,57]. These fragile hemodynamics emphasize the importance of ensuring adequate preload and having vasopressors readily available before intubating these patients. Because of these factors, intubation should be performed by the most experienced clinician with consideration of flexible intubating endoscope and surgical airway in appropriate cases [56].

Patients with decompensated hypothyroidism may present with hypotension and poor perfusion. This hypotension may be due to the hypothyroidism or a concomitant adrenal insufficiency that often accompanies decompensated hypothyroidism [23]. Judicious intravenous fluids are recommended, though clinicians should be cautious in the setting of pulmonary edema and low output heart failure. In the hypothyroid state, hypotension may be refractory to fluids and even vasopressor therapy, which should serve as another late diagnostic clue. Patients may not demonstrate an appropriate physiologic response to vasopressor therapy until the administration of thyroid hormone and steroid replacement [58,59].

Due to relative adrenal suppression, hydrocortisone should be administered early in the management course before administration of thyroid hormone. Administration of T3 and T4 without hydrocortisone may precipitate adrenal crisis and worsen patient hemodynamics [23,60]. The recommended dose of hydrocortisone is 100 mg given intravenously (IV) every 8 h, although lower doses are recommended in

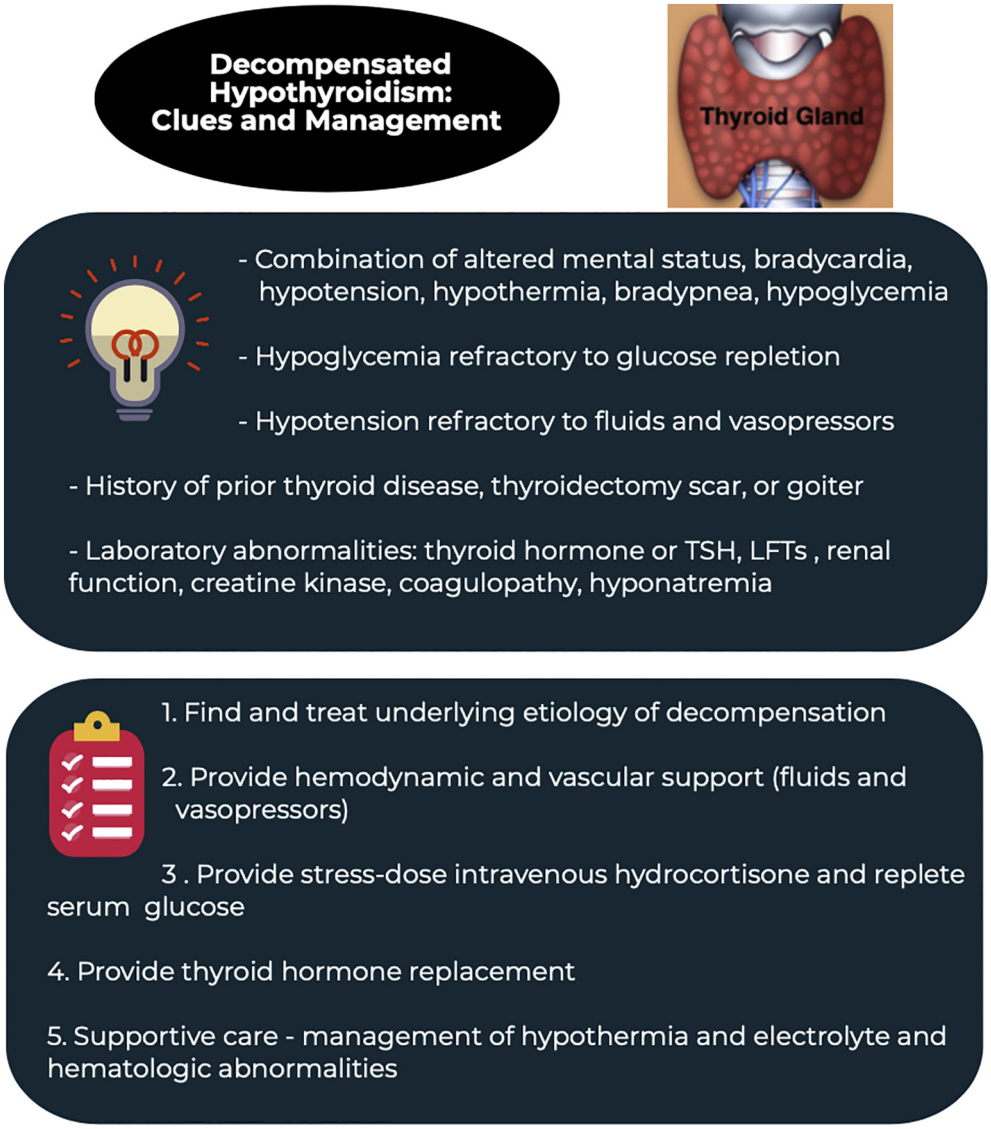
Decompensated Hypothyroidism: Clues and Management
Thyroid Gland
- Combination of altered mental status, bradycardia, hypotension, hypothermia, bradypnea, hypoglycemia
- Hypoglycemia refractory to glucose repletion
- Hypotension refractory to fluids and vasopressors
- History of prior thyroid disease, thyroidectomy scar, or goiter
- Laboratory abnormalities: thyroid hormone or TSH, LFTs , renal function, creatine kinase, coagulopathy, hyponatremia
1. Find and treat underlying etiology of decompensation
2. Provide hemodynamic and vascular support (fluids and vasopressors)
3 . Provide stress-dose intravenous hydrocortisone and replete serum glucose
4. Provide thyroid hormone replacement
5. Supportive care - management of hypothermia and electrolyte and hematologic abnormalities

Fig. 2. Decompensated hypothyroidism diagnosis clues and management priorities.

patients with congestive heart failure in order to reduce the risk of further decompensation due to demand ischemia [60-62].

The type and dose of thyroid hormone repletion remains a controversial topic, as it is necessary to balance administration of the active form of the hormone with the potential for tachydysrhythmias and diastolic hypertension [41,63]. The first-line thyroid replacement is T4 (levothyroxine). As T4 is the inactive form and thus safe for empiric dosing, a 100–500 μg IV loading dose should be administered, followed by 50 μg daily [60]. While these loading doses may be administered via nasogastric tube, there can be erratic absorption due to gastrointestinal edema, ileus, constipation, and gastric atony [60]. T4 is generally safe and effective, though the lower dose range should be considered in older patients or those with history of coronary artery disease or arrhythmia, as well as those patients receiving T3 (liothyronine) [49]. Based on the 2014 guidelines from the American Thyroid Association's Task Force on Thyroid Hormone Replacement, intravenous synthetic T3 can be started with a loading dose of 5–25 μg with a maintenance dose every 8 h at 2.5–10 μg [34]. While T3 is the activated form of thyroid hormone, it may increase the risk of arrhythmia [34]. Lower doses are recommended in patients over 65 years of age, smaller patients, or those with a history of dysrhythmia and coronary artery disease [34]. Studies have demonstrated that combination therapy with lower doses of levothyroxine at 4 μg/kg of ideal body weight and liothyronine at 10 μg every 8–12 h can successfully treat patients with decompensated hypothyroidism [2,18,19,64]. If using the combination therapy strategy, we recommend administering 4 μg/kg IV of ideal body weight of levothyroxine and 10 μg IV of liothyronine. If using monotherapy with levothyroxine alone, we recommend administering 500 μg IV, unless the patient has a smaller body habitus or a history of coronary artery disease or arrhythmia where 400 μg IV is recommended.

It is also important to manage hypothermia, electrolyte abnormalities, and hematologic issues. While patients with decompensated hypothyroidism may present with hypothermia, limited data suggest that passive rewarming may be safer than active rewarming, as the associated peripheral vasodilation could result in circulatory collapse and arrythmia [65]. The authors suggest increasing the environmental temperature and covering the patient with an un-warmed blanket [66]. While not specifically used for rewarming decompensated hypothyroidism patients, high-flow nasal cannula at 60 L/min and 37 degrees Celsius can serve as an adjunct to warm patients from 32 to 37 degrees Celsius in 120 min, demonstrating a possible dual warming and oxygenation adjunct [67]. In cases with severely dampened hemodynamics,

veno-arterial extracorporeal membrane oxygenation has proven successful in providing cardiovascular support when combined with active rewarming [68]. Because of the increased antidiuretic hormone levels present in decompensated hypothyroidism, hyponatremia is commonly seen, as well as hypoglycemia secondary to decreased insulin clearance [69]. Thus, fluid repletion should start with isotonic fluids such as normal saline with dextrose (ie, D5 0.9 normal saline) [58]. Hypotonic fluids should be avoided. Decompensated hypothyroidism may result in acquired von Willebrand syndrome and a decrease in factor levels of V, VII, VIII, IX, X. Empiric desmopressin can be considered for acute bleeding, although the coagulopathy typically corrects with administration of T4 [70,71].

Finally, clinicians must treat the underlying inciting event, which may include infection, environmental exposures, myocardial infarction, congestive heart failure, stroke, gastrointestinal bleeding, surgery, burns, intoxications, or medications. The features of decompensated hypothyroidism closely mimic or can be precipitated by sepsis. Therefore, obtaining cultures and administering broad spectrum antibiotics is recommended in hemodynamically unstable patients or those without a clear etiology of decompensated hypothyroidism.

3.5. Disposition

Because of the associated morbidity and mortality, these patients require close monitoring. Therefore, admission to an intensive care unit is recommended.

4. Conclusions

Decompensated hypothyroidism is a dangerous condition with the potential for significant morbidity and mortality. Clinicians should consider this in patients who are altered, hypothermic, or have refractory hypotension or hypoglycemia. While free T4 is diagnostic of hypothyroidism, it is important to consider the overall clinical picture. Clinicians should provide both adrenal and thyroid supplementation while resuscitating and consider early use of vasopressors. It is important for emergency clinicians to be aware of the evaluation and management of this condition.

Declaration of Competing Interest

None.

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References

[1] Rodríguez I, Fluiters E, Pérez-Méndez LF, Luna R, Páramo C, García-Mayor RV. Factors associated with mortality of patients with myxoedema coma: prospective study in 11 cases treated in a single institution. J Endocrinol. 2004;180(2):347–50.
[2] Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical characteristics and outcomes of myxedema coma: analysis of a national inpatient database in Japan. J Epidemiol. 2017;27(3):117–22.
[3] Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39–51.
[4] Bailes BK. Hypothyroidism in elderly patients. AORN J. 1999;69(5):1026–30.
[5] Jordan RM. Myxedema coma. Pathophysiology, therapy, and factors affecting prognosis. Med Clin North Am. 1995;79(1):185–94.
[6] Yamamoto T, Fukuyama J, Fujiyoshi A. Factors associated with mortality of myxedema coma: report of eight cases and literature survey. Thyroid. 1999;9(12):1167–74.
[7] Dutta P, Bhansali A, Masoodi SR, Bhadada S, Sharma N, Rajput R. Predictors of outcome in myxoedema coma: a study from a tertiary care Centre. Crit Care. 2008;12(1):R1.
[8] Magner JA. Thyroid-stimulating hormone: biosynthesis, cell biology, and bioactivity. Endocr Rev. 1990;11(2):354–85.
[9] Engler D, Burger AG. The deiodination of the iodothyronines and of their derivatives in man. Endocr Rev. 1984;5(2):151–84.
[10] Pilo A, Iervasi G, Vitek F, Ferdeghini M, Cazzuola F, Bianchi R. Thyroidal and peripheral production of 3,5,3′-triiodothyronine in humans by multicompartmental analysis. Am J Physiol. 1990;258(4 Pt 1):E715–26.
[11] Wiersinga WM, Duntas L, Fadeyev V, Nygaard B, Vanderpump MP. 2012 ETA guidelines: the use of L-T4 + L-T3 in the treatment of hypothyroidism. Eur Thyroid J. 2012;1(2):55–71.
[12] Mendel CM, Weisiger RA, Jones AL, Cavalieri RR. Thyroid hormone-binding proteins in plasma facilitate uniform distribution of thyroxine within tissues: a perfused rat liver study. Endocrinology. 1987;120(5):1742–9.
[13] Chiovato L, Magri F, Carlé A. Hypothyroidism in context: where We've been and where We're going. Adv Ther. 2019;36(Suppl. 2):47–58.
[14] Shupnik MA, Ridgway EC, Chin WW. Molecular biology of thyrotropin. Endocr Rev. 1989;10(4):459–75.
[15] Villalba NL, Zulfiqar AA, Saint-Mezard V, et al. Myxedema coma: four patients diagnosed at the internal medicine department of the Dr. Negrin University Hospital in Spain. Pan Afr Med J. 2019;34:7.
[16] Jose M, Amir S, Desai R. Chronic Sheehan's syndrome - a differential to be considered in clinical practice in women with a history of postpartum hemorrhage. Cureus. 2019;11(12):e6290.
[17] Nguyen CT, Mestman JH. Postpartum thyroiditis. Clin Obstet Gynecol. 2019;62(2):359–64.
[18] Wartofsky L. Myxedema coma. Endocrinol Metab Clin North Am. 2006;35(4):687–98 vii–viii.
[19] Mathew V, Misgar RA, Ghosh S, et al. Myxedema coma: a new look into an old crisis. J Thyroid Res. 2011;2011:493462.
[20] Marshall LL. Gastrointestinal bleeding and possible hypothyroidism. Consult Pharm. 2012;27(3):180–8.
[21] Hostiuc S, Capatina CO, Sinescu CJ, Hostiuc M. Lethal pulmonary thromboembolism associated with decreased thyroid hormone levels. Arch Endocrinol Metab. 2015;59(4):355–8.
[22] Sawagashira R, Sasagawa Y, Matsukura M, Takamaru Y. Case of myxedema coma induced by lithium carbonate in a patient with schizophrenia. Psychiatry Clin Neurosci. 2018;72(2):131.
[23] Hawatmeh A, Thawabi M, Abuarqoub A, Shamoon F. Amiodarone induced myxedema coma: two case reports and literature review. Heart Lung. 2018;47(4):429–31.
[24] Markou K, Georgopoulos N, Kyriazopoulou V, Vagenakis AG. Iodine-induced hypothyroidism. Thyroid. 2001;11(5):501–10.
[25] Masamune T, Matsukawa T. Abnormality of thyroid function. Masui. 2010;59(7):879–82.
[26] Church CO, Callen EC. Myxedema coma associated with combination aripiprazole and sertraline therapy. Ann Pharmacother. 2009;43(12):2113–6.
[27] Hamed SA. The effect of antiepileptic drugs on thyroid hormonal function: causes and implications. Expert Rev Clin Pharmacol. 2015;8(6):741–50.
[28] Aziz K, Shahbaz A, Umair M, Sachmechi I. Avelumab inducing hypothyroidism and hypoadrenalism: a case report and review of literature. EXCLI J. 2018;17:526–30.
[29] Thambidorai SK, Sankarapandian BM, Bandara M, Korlakunta HL, Denney SD, Khan IA. Furosemide-induced recurrent syncope in myxedema. Int J Cardiol. 2005;102(1):157.
[30] Tsai SL, Lin CC, Lin CY, Keng-Wei C, Chien CY. Comatose patient with hypothermia, dyspnea, and general edema in the emergency department: a case report. J Int Med Res. 2018;46(10):4338–42.
[31] Chu M, Seltzer TF. Myxedema coma induced by ingestion of raw bok choy. N Engl J Med. 2010;362(20):1945–6.
[32] Chiong YV, Bammerlin E, Mariash CN. Development of an objective tool for the diagnosis of myxedema coma. Transl Res. 2015;166(3):233–43.
[33] Forester CF. Coma in myxedema. Report of a case and review of the world literature. Arch Intern Med. 1963;111:734–43.
[34] Jonklaas J, Bianco AC, Bauer AJ, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670–751.
[35] Smith TJ, Bahn RS, Gorman CA. Connective tissue, glycosaminoglycans, and diseases of the thyroid. Endocr Rev. 1989;10(3):366–91.
[36] Klubo-Gwiezdzinska J, Wartofsky L. Thyroid emergencies. Med Clin North Am. 2012;96(2):385–403.
[37] Ladenson PW, Goldenheim PD, Ridgway EC. Prediction and reversal of blunted ventilatory responsiveness in patients with hypothyroidism. Am J Med. 1988;84(5):877–83.
[38] Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV. Ventilatory control in myxedema and hypothyroidism. N Engl J Med. 1975;292(13):662–5.
[39] Salomo LH, Laursen AH, Reiter N, Feldt-Rasmussen U. Myxoedema coma: an almost forgotten, yet still existing cause of multiorgan failure. BMJ Case Rep. 2014;2014.

[40] Ekka M, Ali I, Aggarwal P, Jamshed N. Cardiac tamponade as initial presenting feature of primary hypothyroidism in the ED. Am J Emerg Med. 2014;32(6) 683.e681–683.
[41] Majid-Moosa A, Schussler JM, Mora A. Myxedema coma with cardiac tamponade and severe cardiomyopathy. Proc (Bayl Univ Med Cent). 2015;28(4):509–11.
[42] Zhang Y, Post WS, Cheng A, Blasco-Colmenares E, Tomaselli GF, Guallar E. Thyroid hormones and electrocardiographic parameters: findings from the third national health and nutrition examination survey. PLoS One. 2013;8(4):e59489.
[43] Montenegro J, González O, Saracho R, Aguirre R, González O, Martínez I. Changes in renal function in primary hypothyroidism. Am J Kidney Dis. 1996;27(2):195–8.
[44] Arnautovic JZ, Connor-Schuler R, Ip R. Mechanical circulatory support in management of cardiogenic shock and myxedema coma. Case Rep Cardiol. 2019;2019:2595736.
[45] Burkholder DB, Klaas JP, Kumar N, Boes CJ. The origin of Woltman's sign of myxoedema. J Clin Neurosci. 2013;20(9):1204–6.
[46] Parikh N, Sharma P, Parmar C. A case report on myxedema madness: curable psychosis. Indian J Psychol Med. 2014;36(1):80–1.
[47] Peritogiannis V, Bolosi M, Lixouriotis C, Rizos DV. Recent insights on prevalence and corelations of hypoactive delirium. Behav Neurol. 2015;2015:416792.
[48] Jansen HJ, Doebé SR, Louwerse ES, van der Linden JC, Netten PM. Status epilepticus caused by a myxoedema coma. Neth J Med. 2006;64(6):202–5.
[49] Dubbs SB, Spangler R. Hypothyroidism: causes, killers, and life-saving treatments. Emerg Med Clin North Am. 2014;32(2):303–17.
[50] Pereira VG, Haron ES, Lima-Neto N, Medeiros-Neto GA. Management of myxedema coma: report on three successfully treated cases with nasogastric or intravenous administration of triiodothyronine. J Endocrinol Invest. 1982;5(5):331–4.
[51] Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". Endocr Rev. 1982;3(2):164–217.
[52] Zondek H. The electrocardiogram in myxoedema. Br Heart J. 1964;26(2):227–32.
[53] Polikar R, Burger AG, Scherrer U, Nicod P. The thyroid and the heart. Circulation. 1993;87(5):1435–41.
[54] Munir A. Myxedema Coma. J Ayub Med Coll Abbottabad. 2018;30(1):119–20.
[55] Attal P, Chanson P. Endocrine aspects of obstructive sleep apnea. J Clin Endocrinol Metab. 2010;95(2):483–95.
[56] Lee CH, Wira CR. Severe angioedema in myxedema coma: a difficult airway in a rare endocrine emergency. Am J Emerg Med. 2009;27(8) 1021.e1021–1022.
[57] Kirsch M, Rimpau C, Nickel CH, Baier P. Intracerebral bleeding and massive pericardial effusion as presenting symptoms of myxedema crisis. Case Rep Emerg Med. 2017;2017:8512147.
[58] Smallridge RC. Metabolic and anatomic thyroid emergencies: a review. Crit Care Med. 1992;20(2):276–91.
[59] Ringel MD. Management of hypothyroidism and hyperthyroidism in the intensive care unit. Crit Care Clin. 2001;17(1):59–74.
[60] Hampton J. Thyroid gland disorder emergencies: thyroid storm and myxedema coma. AACN Adv Crit Care. 2013;24(3):325–32.
[61] Chaudhry MA, Grazette L, Fong MW. Myxedema heart disease: a rare disease entity: case report and brief review of the literature. Curr Hypertens Rev. 2019;15(1):13–6.
[62] Grais IM, Sowers JR. Thyroid and the heart. Am J Med. 2014;127(8):691–8.
[63] Hylander B, Rosenqvist U. Treatment of myxoedema coma–factors associated with fatal outcome. Acta Endocrinol. 1985;108(1):65–71.
[64] Ueda K, Kiyota A, Tsuchida M, Okazaki M, Ozaki N. Successful treatment of myxedema coma with a combination of levothyroxine and liothyronine. Endocr J. 2019;66(5):469–74.
[65] Myers L, Hays J. Myxedema coma. Crit Care Clin. 1991;7(1):43–56.
[66] Reinhardt W, Mann K. Incidence, clinical picture and treatment of hypothyroid coma. Results of a survey. Med Klin (Munich). 1997;92(9):521–4.
[67] Gilardi E, Petrucci M, Sabia L, Wolde Sellasie K, Grieco DL, Pennisi MA. High-flow nasal cannula for body rewarming in hypothermia. Crit Care. 2020;24(1):122.
[68] Kogan A, Kassif Y, Shadel M, et al. Severe hypothermia in myxoedema coma: a rewarming by extracorporeal circulation. Emerg Med Australas. 2011;23(6):773–5.
[69] Kalra S, Unnikrishnan AG, Sahay R. The hypoglycemic side of hypothyroidism. Indian J Endocrinol Metab. 2014;18(1):1–3.
[70] Michiels JJ, Schroyens W, Berneman Z, van der Planken M. Acquired von Willebrand syndrome type 1 in hypothyroidism: reversal after treatment with thyroxine. Clin Appl Thromb Hemost. 2001;7(2):113–5.
[71] Nitu-Whalley IC, Lee CA. Acquired von Willebrand syndrome - report of 10 cases and review of the literature. Haemophilia. 1995;5(5):318–26.